# CHAPTER IX: UNDERSTANDING AND IMPROVING CURRENT DRUGS: HEPARIN

So, what I'm now going to do is change gears and go through a few examples to give you a diversity of the challenges, possibilities, opportunities, with the idea of what we are trying to do to bring these kinds of thinking, these kinds of technologies to really not only understand the biology, but how to improve on some of the existing problems and challenges with the drugs that are on the current market.

And, I'm going to use heparin because heparin, in many ways, could be viewed as probably the most interesting natural product, because it's been around for the last seventy to eighty years, was discovered by accident to have an anticoagulant function, used in the clinic as the most safe natural product with minimal modification, but, yet, it's a fairly complex mixture that, as I showed you with the few earlier slides, we truly don't understand some of the nuances of how various sequences correlate to function.

So, I'm going to focus on an area of application, which is ACS, that all of you might know, which is essentially acute coronary syndrome, which essentially comprises the unstable angina and acute MI, where the arthrosclerotic part, leading to a rupture, eventually lead to a clot formation and in anything downstream. And, heparin is the drug of choice that's being used in the ACS setting, because of its anticoagulant function.

So, when you go into an emergency room, a patient A patient entering the ER with ACS is given either heparin, which is a fairly complex, highly heterogeneous mixture, or low molecular weight heparin, which is essentially putting heparin in a blender and trying to reduce its poly disbursity to relatively, to a smaller extent. And, the

idea is how do you look at the variety of downstream events of medical management, PCR, or CABG, because, ACS is probably the most challenging and difficult management that you could ever think of. Because, the attributes that you need to have for this is enhance artero efficacy, full reversibility, few bleeding complications, ability to monitor your drug, and, finally, a predictable...an ease of use. And, these are fairly difficult things to achieve and, in some sense, heparin has, because of its historical role, been able to play a satisfactory role in the ER.

So, when we ask the question, how does this really work? How does this complex mixture, where ten percent of this mixture essentially has a sequence that binds to anti thrombin three, which eventually binds to thrombin, as a way to dramatically activate the clotting cascade as a way to inhibit the clot formation that is downstream in ACS?

And, the idea is the following. Here's the basic pathway. There are two pathways. The intrinsic pathway and the extrinsic pathway. One by tissue damage, the other by trauma, that converge and heparin plays a role in this point that I'm going to come to in a minute, it's activated by prothrombin to thrombin, and thrombin feeds back a variety of these upstream events to eventually regulate the clot formation. And, what heparin and low molecular weight heparins do is that they regulate the anti-thrombin by dramatically forming a complex and kinetically affecting the convergent common pathway, and hence thrombin, and feedback into a variety of these loops as a way to regulate the process of coagulation.

It's important to point out that one of the limitations of heparin is it does not really touch the common pathway and the extrinsic pathway, which is one of the serious limitations of this molecule in the clinic.

So, what we came about, and I'm going to come to that in a minute or two, is using a variety of our techniques of getting to the structure function of these mixtures, understanding the distribution of these moieties in this mixture, how to tailor make a molecule that could not only access all these different pathways, but also address the issues of some of the limitations that I spoke about.

So, the point being could you then design a molecule that would not only activate these two common pathways, but, eventually, regulate the thrombin by blocking the entire cascade.

The long and short of it is, because we developed a whole host of enzymes and these were the earlier studies that my laboratory did through funding from NIGMS, was generate a set of enzymes that very specifically access the anti-thrombin three binding side in this mixture. And, since we couldn't study this mixture, you know, in terms of the various chemical components, we were able to generate a specific set of heparin moieties that have both the XA and IIA binding side. It also had a constant ratio between these two, which is very important. It had the reduced poly disbursity that limits both heparin and low molecular weight heparin.

In many ways, you could view this as it had the best of attributes of heparin and low molecular weight heparin, and it removed the bad attributes of both heparin and low molecular weight heparin, so it eliminated unnecessary sequences or sequences that caused side effects.

So, we show, through both, you know, rapid model, in terms of increasing the arterial efficacy, but, most importantly, the ability to neutralize this, because, that is one of the key things that is needed in the ACS setting, where this particular molecule was fairly effectively neutralized, compatible to un-fractionated heparin, but low molecular weight heparin does not. Low molecular weight heparin cannot be monitored. Heparin can be. Low molecular weight heparin cannot be neutralized, but heparin can. But, heparin has bleeding problems.

So, the long and short of it is here's a summary of what we try to generate, compared to the other molecules that are there in the clinic, and showing that you can actually access this complex mixture, and really dial in, if you will, attributes that you really want into it, such as enhanced efficacy, full reversibility, few bleeding complications, ability to monitor, and to be able to have an ease of use with regard to predictable PK, because heparin truly is limited by that.

So, the point really being, once you understand the structure activity, once you have the tools and techniques to be able to think about this problem in this fashion, you can take current molecules, and truly improve them, and get to the heart of the structure-function relationship.

So, this particular molecule and IND has been filed and the first patient was dosed earlier this month. And, the clinical trials are ongoing to really evaluate whether this would be a viable candidate for ACS setting of replacing heparin.